Pharmaceutical Regulatory Affairs 2012: Design, Synthesis and Biological Evaluation of Novel N-1 and C-3 Functionalized Isatin Derivatives as FAAH Inhibitors -Indian Institute of Technology, Varanasi

Shivani Jaiswala Senthil Raja
Indian Institute of Technology, Varanasi, E-mail: ShivaniJaiswala@gmail.com

Abstract

Fatty acid amide hydrolase (FAAH) inhibition activity a valuable strategy for the treatment of several CNS disorders, including pain, depression, and anxiety. In the search for better FAAH inhibitors with potent activity; based on our previous isatin based lead compound 8c, we designed and synthesized a series of structural analogs of 8c by varying the substitutions at both N-1 and C-3 of the isatin scaffold. The synthesized compounds tested for In vitro FAAH inhibition activity. All tested compounds showed the inhibition against FAAH in nanomolar to micromolar range 6.7 nM to 207.8 µM. Compound 5e (Z)-3-((1H-benzo[d]imidazol-2-yl)imino)-1- allylindolin-2-one with IC50 value of 0.006734±0.002 µM emerged as the most potent reversible inhibitor with ki value 5 nM, examined towards FAAH with almost 1500 times more potency than our previous lead 8c (IC50 =1.49 ± 0.03µM). Molecular docking studies supported the experimental results revealing that all compounds well-occupied the enzymatic cleft with optimal binding orientation and interactions within the active site of FAAH. Moreover, Compound 5e was found to be significantly more potent anxiolytic as well as potent antidepressant as compared to reference drug citalopram and diazepam respectively. Lead compound 5e was also found nonneurotoxic and satisfactory drug-like characteristics and ADMET properties and thus considered for further evaluation. Fig. Docked conformations of most active compound 5e within active site of FAAH. The five-membered pyrrolidine ring is one of the nitrogen heterocycles used widely by medicinal chemists to obtain compounds for the treatment of human diseases. The great interest in this saturated scaffold is enhanced by (1) the possibility to efficiently explore the pharmacophore space due to sp3-hybridization, (2) the contribution to the stereochemistry of the molecule, (3) and the increased three-dimensional (3D) coverage due to the non-planarity of the ring—a phenomenon called "pseudorotation". In this review, we report bioactive molecules with target selectivity characterized by the pyrrolidine ring and its derivatives, including pyrrolizines, pyrrolidine-2-one, pyrrolidine-2,5-diones and prolinol described in the literature from 2015 to date. After a comparison of the physicochemical parameters of pyrrolidine with the parent aromatic pyrrole and cyclopentane, we investigate the influence of steric factors on biological activity, also describing the structure–activity relationship (SAR) of the studied compounds. To aid the reader's approach to reading the manuscript, we have planned the review on the basis of the synthetic strategies used: (1) ring construction from different cyclic or acyclic precursors, reporting the synthesis and the reaction conditions, or (2) functionalization of preformed pyrrolidine rings, e.g., proline derivatives. Since one of the most significant features of the pyrrolidine ring is the stereogenicity of carbons, we highlight how the different stereoisomers and the spatial orientation of substituents can lead to a different biological profile of drug candidates, due to the different binding mode to enantioselective proteins. We believe that this work can guide medicinal chemists to the best approach in the design of new pyrrolidine compounds with different biological profiles.